

WHAT IS CLAIMED IS:

1. A method of determining the sequence of bases of a DNA or RNA, comprising the steps of:

producing a magnified image of an elongated single-chain DNA or RNA by a transmission electron microscope; and

discriminating base-specific labels of heavy elements using said magnified image.

2. A method of determining the sequence of bases of a DNA or RNA, comprising the steps of:

(a) forming a support film, on which an elongated single-chain DNA or RNA is held, on an electron microscope grid;

(b) treating bases of the elongated single-chain DNA or RNA on the support film formed on said microscope grid with base derivatives each containing a heavy element or elements to form base pairs, thus forming base-specific labels of heavy elements; and

(c) observing the elongated single-chain DNA or RNA through a transmission electron microscope and discriminating said base-specific labels of heavy elements using an obtained magnified image.

3. A method of determining the sequence of bases as set forth in claim 1 or 2, wherein a phase-contrast electron microscope or complex electron microscope is used as said transmission electron microscope.

4. A method of determining the sequence of bases as set forth in claim 2, wherein said support film that holds the elongated single-chain DNA or RNA is made of organic thin films such as the LB films and a protein-denatured film, aminated amorphous carbon film, or amorphous aluminum film.

5. A method of determining the sequence of bases as set forth in claim 1 or 2, further including the step of obtaining the elongated single-chain DNA or RNA by rapid expansion of a DNA or RNA solution on a water surface as a method of elongating the single-chain DNA or RNA.

6. A method of determining the sequence of bases as set forth in claim 1 or 2, wherein base-specific labels of heavy elements are base pairs A-U\*, T-A\*, G-C\*, C-G\*, or U-A\* of bases (A, T, G, C) on a single-chain DNA or bases (A, U, G, C) on an RNA with bases labeled with heavy elements (A\*, U\*, G\*, C\*).

7. A method of determining the sequence of bases as set forth in claim 1 or 2, wherein the base derivatives including heavy elements for forming base-specific labels of heavy elements are bases labeled with heavy elements to which heavy element complexes are bonded, whereby the bases are labeled.

8. A method of determining the sequence of bases as set forth in claim 6, wherein the base derivatives including heavy elements for forming base-specific labels of heavy elements are bases labeled with heavy elements to which heavy element complexes are bonded, whereby the bases are labeled.

9. A method of determining the sequence of bases as set forth in claim 7, wherein binding sites at which the heavy element complexes are bonded to the bases are nitrogen atoms at 7- and/or 9-positions for cases of adenine(A) and guanine(G) and nitrogen atom at 1-position for cases of uracil(U) and cytosine(C).

10. A method of determining the sequence of bases as set forth in claim 7, wherein the heavy elements of the heavy element complexes are a combination of four kinds of elements having atomic numbers which are greater than 25 and spaced apart from each other by more than 15.

11. A method of determining the sequence of bases as set forth in claim 9, wherein the heavy elements of the heavy element complexes are a combination of four kinds of elements having atomic numbers which are greater than 25 and spaced apart from each other by more than 15.

12. A method of determining the sequence of bases as set forth in claim 10, wherein the combination of the four kinds of elements are "Pt, Eu, Pd, Co", "U, Os, Pd, Fe", "Hg, Gd, Cd, Zn", and "Ac, W, Mo, Mn".

13. A method of determining the sequence of bases as set forth in claim 12, wherein the heavy element complexes including four kinds of metal elements Pt, Eu, Pd, and Co correspond to G\*, C\*, A\*, and U\* in an unordered manner.

14. A method of determining the sequence of bases as set forth in claim 7, wherein each of said heavy element complexes is a complex where a molecule contains one heavy element or is a metal element cluster where a molecule contains plural heavy atoms.

15. A method of determining the sequence of bases as set forth in claim 14, wherein the metal cluster complex where a molecule contains plural heavy atoms is a complex which includes four heavy atoms and to which an iron-sulfur cluster is bonded.

16. A method of determining the sequence of bases as set forth in claim 6, wherein the bases (A\*, U\*, G\*, C\*) labeled with heavy elements are heavy element-labeled bases which are partially substituted by at least one substitutive group selected from the group consisting of alkyl groups, cyclohexyl groups, halogen groups, phenyl groups, and phenol groups and have enhanced dissolubility into organic solvents.

17. A method of determining the sequence of bases as set forth in claim 7, wherein the bases (A\*, U\*, G\*, C\*) labeled with heavy elements are heavy element-labeled bases which are partially substituted by at least one substitutive group selected from the group consisting of alkyl groups, cyclohexyl groups, halogen groups, phenyl groups, and phenol groups and have enhanced dissolubility into organic solvents.

18. A method of determining the sequence of bases as set forth in claim 16, wherein substitution sites are 2- and/or 8-positions in case of adenine(A), 8-position in case of guanine(G), and 5- and 6-positions in cases of uracil(U) and cytosine(C).

19. A method of determining the sequence of bases as set forth in claim 17, wherein substitution sites are 2- and/or 8-positions in case of adenine(A), 8-position in case of guanine(G), and 5- and 6-positions in cases of uracil(U) and cytosine(C).

20. A method of determining the sequence of bases as set forth in claim 6, wherein the bases (A\*, U\*, G\*, C\*) labeled with heavy elements are heavy element-labeled bases which are partially substituted by at least one substitutive group selected from the group consisting of halogen groups and amino groups, whereby the selectivity of pair bonding with respect to bases on the DNA or RNA is enhanced.

21. A method of determining the sequence of bases as set forth in claim 7, wherein the bases (A\*, U\*, G\*, C\*) labeled with heavy elements are heavy element-labeled bases which are partially substituted by at least one substitutive group selected from the group consisting of halogen groups and amino groups, whereby the selectivity of pair bonding with respect to bases on the DNA or RNA is enhanced.

22. A method of determining the sequence of bases as set forth in claim 20, wherein substitution sites are 2- and/or 8-positions in cases of adenine(A), 8-position in case of guanine(G), and 5- and 6-positions in cases of uracil(U) and cytosine(C).

23. A method of determining the sequence of bases as set forth in claim 21, wherein substitution sites are 2- and/or 8-positions in cases of adenine(A), 8-position in case of guanine(G), and 5- and 6-positions in cases of uracil(U) and cytosine(C).

24. A method of determining the sequence of bases as set forth in claim 2, wherein base pairs are formed in an organic solvent.

25. A method of determining the sequence of bases as set forth in claim 6, wherein base pairs are formed in an organic solvent.

26. A method of determining the sequence of bases as set forth in claim 7, wherein base pairs are formed in an organic solvent.

27. A method of determining the sequence of bases as set forth in claim 24, wherein the organic solvent is selected from organic solvents having dielectric constants of less than 10.

28. A method of determining the sequence of bases as set forth in claim 25, wherein the organic solvent is selected from organic solvents having dielectric constants of less than 10.

29. A method of determining the sequence of bases as set forth in claim 26, wherein the organic solvent is selected from organic solvents having dielectric constants of less than 10.

30. A method of determining the sequence of bases as set forth in claim 1 or 2, wherein a high-density, low-noise recording medium having a wide dynamic range is used as a recording medium for recording the magnified image produced by the transmission electron microscope.

31. A method of determining the sequence of bases as set forth in claim 30, wherein said high-density, low-noise recording medium having a wide dynamic range is a CCD or an imaging plate (IP).

32. A transmission electron microscope for use in a method of determining the sequence of bases as set forth in claim 1 or 2, comprising a tilt imaging system for obtaining an image from which overlap of intersecting portions of the chain on a microscope image is removed, whereby the sequence of the bases can be determined if the DNA or RNA has such intersecting portions.

33. A transmission electron microscope for use in a method of determining the sequence of bases as set forth in claim 1 or 2, wherein said transmission electron microscope is a phase-contrast electron microscope or complex electron microscope loaded with analysis software for discriminating heavy elements using the electron microscope.

34. A DNA sequencer comprising:

a transmission electron microscope for discriminating base-specific labels of heavy elements and producing a magnified image; and

an analyzer for analyzing said magnified image to determine the sequence of bases of DNA or RNA.

Patent Application No. 2004/0100000